UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

May 27th, 2014

SUBJECT: **Tebuthiuron:** Summary of Hazard and Science Policy Council (HASPOC) Meeting of March 13, 2014: Recommendations on the need for Acute and Subchronic Neurotoxicity Studies, a Subchronic Inhalation Study, and Chronic Toxicity/Carcinogenicity studies in Rodents.

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TO: Chris Schlosser, Toxicologist
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MEETING ATTENDEES:

HASPOC Members: Anna Lowit, Elissa Reaves, John Kough, Jonathan Chen, Jeff Evans, Jeff Dawson, Michael Metzger, P.V. Shah, Ray Kent, Jonathan Leshin, Kristin Rury, Uma Habiba, Monique Perron

Presenter: Chris Schlosser

Other Attendees: Lata Ven, Yvonne Barnes, Sheila Piper, Billy Smith

I. PURPOSE OF MEETING:

The Risk Assessment Branch VI (RAB VI) tebuthiuron team is preparing the Registration Review Risk Assessment for tebuthiuron. The team requested that Hazard and Science Policy Council (HASPOC) consider the need for a rat 28- or 90-day inhalation toxicity study (870.3465), and neurotoxicity screening battery (870.6200) for tebuthiuron. There are at present no waiver requests from the Registrant but these studies are required to support registration under the current 40 CFR Part 158 Toxicology Data requirements. In addition, the risk assessment team requested that HASPOC to reassess the need for a combined chronic toxicity/carcinogenicity assay in the rats (870.4300), carcinogenicity study in the mouse (870.4200). These studies were considered to be unacceptable, and were previously waived in a 2005 response to comments (TXR #0054232). A scoping document was completed in March 2009, and requested neurotoxicity and immunotoxicity studies. The lack of an inhalation toxicity study was not identified in the scoping document (Barnes et al. 2009). Since the scoping document an immunotoxicity study has been submitted.

II. SUMMARY OF USE PROFILE, EXPOSURE, & HAZARD CONSIDERATIONS:

a. Use Profile

Tebuthiuron is an herbicide that controls broadleaf and grassy weeds and woody plants in pastureland/rangeland, and non-crop industrial areas such as highways, fence rows, firebreaks, utility rights-of-ways, railroad rights-of-ways, and clearings for wildlife habitat. Information provided by registrants estimate that approximately 150,000 – 185,000 lbs of total a.i. was used annually between 2011 and 2013 and that approximately 75% was applied aerially in western states. End-use products are formulated as water dispersible granulars (WDGs), dry flowables (DFs), granulars (Gs), and pellets (Ps) which are applied using aerial, ground, and handheld equipment. The application rates on labels range from 0.6 lb ai/A to 6 lb ai/A with a maximum seasonal rate 6 lb ai/A for spot treatment and 4 lb ai/A for pastureland/rangeland. There is a potential for occupational exposure associated with handler activities (i.e., mixing, loading, and applying). Based on application rates and label information, occupational exposure to tebuthiuron is expected to occur for short-(1 to 30 days) and intermediate-term (1 to 6 months) durations during mixing, loading, applying, and other handling activities. Occupational post-application and chronic exposures are not expected.

The personal protective equipment (PPE) is inconsistent across labels. The DF and WDG formulations provide personal PPE language directing occupational handlers to wear baseline clothing (i.e., long sleeved shirts, long pants, shoes, and socks), and chemical resistant gloves made of waterproof material. Two of the three pelleted formulations do not have any PPE listed on the labels and all but one granular formulation require the use of a NIOSH filter respirator as well as the baseline dermal clothing and chemical resistant gloves. Protective eyewear is also listed on some of the labels. While there are no agricultural food crops currently registered, the current restricted entry interval (REI) for any harvesting of hay from a pastureland use site is 12 hours based on the acute toxicity of tebuthiuron.

b. Toxicity Profile:

Tebuthiuron is a non-selective substituted urea herbicide. Its herbicidal mode of action is the inhibition of photosynthesis. The most consistent toxicological effect across the database is decreased body weight, occurring in rats, rabbits and dogs. Tebuthiuron targets the liver in dogs, characterized by significant increases in liver weights, alanine aminotransferase (ALT), and alkaline phosphatase (ALP). Dogs also displayed clinical signs of toxicity including anorexia and diarrhea. In rats, vacuolization of pancreatic acinar cells were observed at high-doses in both chronic and sub-chronic toxicity studies. However, these effects were characterized as slight and only affecting few cells. In rabbits, significant decreases in fetal body weights were observed at a dose that also resulted in increases in early resorptions, at doses of 25 mg/kg/day and above. In rats, decreases in pup body weights were observed on PND 21 in F1 and F2 generation pups at 26 mg/kg/day. These effects occurred in the presence of decreases in female F1 adult bodyweights.

The acute toxicity studies indicate that tebuthiuron is more toxic following oral (Category II) exposure than either dermal (Category IV) or inhalation (Category III) exposure. This is supported by ADME data, indicating complete and rapid absorption of tebuthiuron following oral administration. Tebuthiuron is not an eye or skin irritant and not a skin sensitizer. No evidence reproductive, neurological or immunotoxicity were identified in the database.

c. Endpoints and Risk Assessment Considerations

For acute dietary assessment of females 13 - 49, the developmental toxicity study in rabbits was selected with a NOAEL of 10 mg/kg/day for dams and pups. The LOAEL is 25 mg/kg/day for dams and pups based on early resorptions and decreased fetal body weights. The agency considers early resorptions as a potential acute effect and therefore this study is considered to be appropriate for acute dietary endpoint selection for females of child-bearing age. No appropriate toxicological endpoints attributable to a single exposure were identified for the general population.

For short-term incidental oral exposure (1-30 days), the 2-generation reproductive toxicity study in rats was selected with a NOAEL of 14 mg/kg/day. The LOAEL is 26 mg/kg/day based on decreased body weights in F1 females (13%) and decreased pup body weights on PND 21 in the F1 and F2 generation (5-8%). The endpoint of concern in this study is appropriate for the population (infant and children) and the duration of concern. Intermediate and long-term exposure are not expected based on current use patterns; therefore, endpoints for risk assessment for intermediate and long-term incidental oral exposure are not required.

A dermal toxicity study in adult animals where no effects were observed up to the limit dose is available. However, for short and intermediate-term dermal exposure, the 2-generation reproductive toxicity study in rats was selected with a NOAEL of 14 mg/kg/day. The LOAEL is 26 mg/kg/day based on decreased body weights in F1 females (13%) and decreased pup body weights on PND 21 in the F1 and F2 generation (5-8%). A dermal risk assessment is being conducted. Although no dermal absorption data are available, the physical properties of the chemical support the potential for dermal absorption and the existing dermal study conducted did

not measure the adverse outcome (resorptions) for the PODs for pregnant females. As discussed above, the 2-generation reproductive toxicity study with a NOAEL of 14 mg/kg was selected as it is protective of both developmental effects in rabbits and offspring effects observed in the rats. There is no proposed long-term use; therefore, risk assessment for long-term dermal exposure is not required.

Occupational exposures have not been considered quantitatively in any existing risk assessment to date for tebuthiuron; the 2014 preliminary risk assessment to support the registration review of tebuthiuron will evaluate occupational exposures. In addition, the 2014 preliminary risk assessment will consider potential for drinking water exposure from the pasture/rangeland uses.

III. STUDY WAIVER REQUESTS

a. Chronic Toxicity and Carcinogenicity Toxicity Studies

In the combined chronic toxicity/carcinogenicity study in rats, the only treatment-related systemic effect was reported to be decreased terminal body weights (10-19%) in females at LOAEL/NOAEL of 40 and 80 mg/kg/day. Doses tested up to 80 mg/kg in the rat did not show carcinogenic potential. In 2004, the Dose Adequacy Review Team (DART) concluded that the highest dose tested of 80 mg/kg in the chronic rat study was adequate to assess the carcinogenicity of tebuthiuron based on the results of the 90-day rat study (TXR# 0052580). However, the studied was considered to be unacceptable as several major deficiencies were identified including:

- The mortality rate for all groups was high, leaving only 25% or fewer animals in some groups out of an initial number of at least 80 per group.
- Respiratory infections were very prevalent in all groups and may have affected the outcome of the study.
- Summary tables and individual animal data were not available for clinical signs, body weights, body weight gains, food consumption, urinalysis data, and gross findings.

In the mouse carcinogenicity assay, no treatment-related effects were observed at doses of up to 240 mg/kg. At that time, DART determined that the doses tested were not adequate to assess the carcinogenicity of tebuthiuron.

The HASPOC, based on a WOE approach, recommends that the chronic toxicity/carcinogenicity studies **be waived** based on the following considerations:

- The rat is more sensitive than the mouse for the chronic assessment.
- Effects seen in the most sensitive species (rats) and most sensitive sub populations (i.e., F1 offspring/parents) in the two-generation rat study have been used at the point of departure for the chronic assessment.
- Doses from the rat study were considered to be adequate for testing of carcinogenicity.
- New studies would only use doses well above the current POD for the chronic assessment
- Based on current policy (U.S. EPA 2005), even if a new mouse study identified carcinogenicity effects, that finding would not result in the adoption of a quantitative linear assessment of cancer risk due to the negative carcinogenicity finding in the rat study and the lack of a positive finding for genotoxicity.

b. Inhalation Study

Previously, the Office of Pesticide Programs (OPP) used a set of criteria to determine whether an inhalation study could be waived. These criteria considered the scientific information available for the chemical, including: 1) the degree of irritation and corrosivity; 2) volatility; 3) aerosol particle size; and 4) Acute Toxicity Category and extrapolated MOEs (e.g., MOEs 10 times higher than the target). In 2009, OPP developed an issue paper on risk assessment approaches for semi-volatile pesticides. As part of that issue paper, an analytical comparison was conducted of oral and inhalation experimental toxicology studies. In general, this analysis showed that the degree to which oral PODs were protective of potential inhalation toxicity varied. In many cases the oral POD was protective, but in some cases the inhalation PODs were significantly more protective. Currently, OPP uses a weight of the evidence (WOE) approach that builds upon OPP's experience using the criteria listed above and conclusions from the 2009 SAP. As approaches for route-to-route extrapolation continue to evolve and improve, OPP may incorporate additional considerations into the WOE analysis.

Inhalation exposure can be to vapors, droplets, and/or particles/dusts. The form of inhalation exposure is determined by a number of factors including physical-chemical properties, use pattern, and exposure scenarios. OPP's interim WOE approach considers:

1. **Physical-chemical properties:** Tebuthiuron (MW = 228.3 g/mol) has a low vapor pressure of $2x10^{-6}$ mm Hg at 25 °C and a Henry's law constant of 4.9884×10^{-11} atm m^3/mol., which indicates that this chemical is relatively non-volatile under field conditions. These parameters are key considerations with respect to the volatilization after sprays have settled. The low vapor pressure and/or Henry's law constant, however, does not preclude exposure to aerosolized droplets or particles/dusts.

2. **Use pattern & exposure scenarios:** Any application scenario that leads to inhalation exposure to droplets needs to be considered in the WOE analysis for an inhalation toxicology study waiver request. In the case of tebuthiuron, mixing/loading of dry flowable and water dispersible granulars for aerial applications for high acreage (1200 acres) of pastureland/rangeland results in the highest inhalation exposure (MOE = 19).

3. **Specific Toxicological Considerations:** The acute toxicity studies indicate that tebuthiuron has moderate toxicity via inhalation (Category III) exposure.

4. **Margins of Exposure (MOEs):** The MOE estimates for inhalation scenarios were calculated using an oral POD from a 2-generation reproductive toxicity study with a NOAEL of 14 mg/kg/day based on decreased body weights in the F1 and F2 pups and F1 dams. Since an oral dose was selected absorption via inhalation is presumed to be equivalent to oral absorption. This oral toxicity study should be considered in the WOE analysis for an inhalation toxicology study waiver request. In the past, OPP has used MOEs of approximately 10 times higher than the LOC as a benchmark for granting waiver requests. The 2009 analysis suggests this approach is appropriate for most pesticides, but not all. Using this interim WOE approach, MOEs from 10-100 times greater than the LOC will be considered in combination with other factors discussed here.

Occupational handler risk estimates ranged from 19 to 46,000 at baseline inhalation PPE. There are occupational inhalation risk estimates of concern for scenarios; mixing/loading of dry flowable and water dispersible granulars for aerial applications at the rate of 4 lbs ai/A for high acreage (1200 acres) of pastureland/rangeland. While tebuthiuron retreatment intervals (RTI) are once every two to three years and twice every six years intermediate exposure was assessed to account for large agribusiness and/or commercial applicators who may apply a product over a period of weeks (e.g., completing multiple applications for multiple clients within a region). Information provided by registrants estimate that approximately 150,000 – 185,000 lbs of total a.i. was used annually between 2011 and 2013 and that approximately 75% was applied aerially in western states.

The HASPOC, based on a WOE approach, recommends that an inhalation toxicity study for tebuthiuron **be required** for the following reasons: 1) the use of an oral POD results in unacceptable MOEs for workers for aerial applications; and 2) significant aerial application of tebuthiuron is expected based on reported use patterns. HASPOC further recommends that the registrant discuss the protocol for the inhalation with the agency to determine whether or not a special study design to consider pup weight and resorptions is warranted.

c. Acute and Subchronic Neurotoxicity

Acute (ACN) and sub-chronic neurotoxicity (SCN) studies are required in the 2007 revised 40 CFR Part 158 Toxicology Data Requirements because they provide important scientific information on potential nervous system effects from pesticide exposure. These studies can provide data on a wide range of functional tests for evaluating neurotoxicity including sensory effects, neuromuscular effects, learning and memory and histopathology of the nervous system. For picloram, both an ACN and a SCN are not available. With respect to considering whether the ACN and SCN studies should be required for picloram, the HASPOC used the following weight of the evidence (WOE) approach:

1. **Evidence for potential neurotoxicity in the tricyclazole database of toxicology studies:** No evidence of neurotoxicity was observed in the tebuthiuron database.

2. **Evidence for neurotoxicity in the database of other similar chemicals:** No neurotoxicity studies were available for structurally related chemicals.

3. **Risk assessment considerations:** The available data indicate that neurotoxicity is of low concern for tebuthiuron, and the PODs used currently for overall risk assessments are considered protective of any potential neurotoxicity. Using an oral POD, the acute and chronic dietary risk estimates (food only) for tebuthiuron utilize <1% of the aPAD and cPAD, respectively.

The HASPOC, based on a WOE approach, concludes that the ACN and SCN studies **be waived** at this time based on the following: 1) no evidence of neurotoxicity was observed in the database. 3) The primary toxic effect throughout the database is decreased body weights in adult, pre- and post-natal animals. Additionally, an increase early resorptions in rabbits were observed. 3) The ACN and SCN studies are unlikely to provide a lower POD or a more sensitive endpoint than those currently used for risk assessment.

IV. HASPOC CONCLUSIONS

Based on a WOE approach and considering all of the available tebuthiuron hazard and exposure data, the HASPOC has concluded that **chronic/carcinogenicity and acute and subchronic neurotoxicity studies are not needed at this time and that a subchronic inhalation study is needed.**

V. REFERENCES

U.S. EPA. (2005). Guidelines for Carcinogen Risk Assessment. http://www.epa.gov/raf/publications/pdfs/CANCER_GUIDELINES_FINAL_3-25-05.PDF